REMARKS

Claims 1, 3-5, 7-33, 35-36 and 38-45 are pending.

35 U.S.C. § 112 Rejections

Reconsideration is respectfully requested of the rejection of claim 41 under 35 U.S.C. § 112, second paragraph for failing to satisfy the definiteness requirement. Claim 41 has been amended to delete the reference to "said anti-tumor platinum-coordination compound" and replace it with "said aminoglycoside antibiotic." Thus, claim 41 satisfies the definiteness requirement of 35 U.S.C. § 112, second paragraph.

Reconsideration is respectfully requested of the rejection of claims 18-22 under 35 U.S.C. § 112, first paragraph enablement requirement. Claim 18 is directed to a method for reducing the incidence of ototoxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound, the method comprising administering to said patient an effective amount of an otoprotective agent comprising methionine, the protective agent being administered parenterally, orally or topically to the round window membrane. The Office misunderstands the meaning of these claims. The phrase "to the round window membrane" modifies topically only and does not modify parenterally or orally. As the Office points out, there is no way to deliver the protectant agent by oral or parenteral administration to the round window membrane. Thus, a person of ordinary skill would have known that the claim meant there were three methods of administration: (1) parenterally, (2) orally, and (3) topically to the round window membrane. Thus, claims 18-22 satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 102 Rejection

Reconsideration is respectfully requested of the rejection of claims 33, 35, 36, and 38-45 as being anticipated by Furuno et al. (U.S. Patent No. 3,962,429). Claim 33 is directed to methods for reducing the incidence of ototoxicity in a patient undergoing treatment with an aminoglycoside antibiotic, the method comprising administering to said patient an effective amount of an otoprotective agent comprising methionine.

Furuno et al. describe the reduction of aminoglycoside antibiotic side effects of renal toxicity and 8th nerve toxicity by the administration of a glucosaccharide acid with the aminoglycoside antibiotic. Furuno et al. also describe formulations of an aminoglycoside antibiotic, a glucosaccharide acid, and methionine as a stabilizer.

The Furuno reference does not teach treating ototoxicity, the method described treats only renal toxicity and 8th nerve toxicity. Thus, since the Furuno reference does not expressly anticipate claims 33, 35, 36, and 38-45, the Examiner's § 102 rejection must be based on inherency. However, a treatment for ototoxicity cannot be inherent in the Furuno reference unless ototoxicity would have necessarily and inevitably arisen from administration of an aminoglycoside antibiotic. To that end, administration of an inherently ototoxic dosage of an aminoglycoside antibiotic cannot be demonstrated in any method suggested by the Furuno reference. Inherency may not be established if there is only a probability or possibility that a certain result may occur.[1] In the present case, administration of an aminoglycoside antibiotic would not have necessarily and inevitably resulted in the occurrence of ototoxicity in a subject. As explained above, Furuno et al. describe the effects of L-methionine on renal toxicity and 8th nerve toxicity. Furano does not even recognize that ototoxicity is an issue with patients receiving aminoglycoside antibiotics, much less that administration of methionine would have an ameliorative effect. Moreover, even if one skilled in the art were aware from other sources that ototoxicity can arise from administration of an aminoglycoside, there is no disclosure in Furuno from which one skilled in art could conclude that the aminoglycoside treatment in that reference might raise more than a mere possibility of ototoxic effects. In fact, only about 10% of people taking aminoglycoside antibiotics experience ototoxicity, although up to 33% has also been reported in adult patients.[2] Thus, there is not more than a mere possibility that ototoxicity will occur for many therapeutic doses of aminoglycoside antibiotics and ototoxicity certainly does not inevitably or necessarily result upon the administration of aminoglycoside antibiotics in the range of doses disclosed by Furuno et al. Therefore, claim 33, and the claims that depend therefrom satisfy the requirements of 35 U.S.C. § 102(b).

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[1] *In re Oelrich*, 666 F.2d 578.

[2] Wackym PA, Storper IS and Newman AN. Cochlear and Vestibular Ototoxicity. In: Canalis RF and Lambert PR, editors. *The Ear: Comprehensive Otology*. Philadelphia: Lipincott Williams and Wilkins; 2000; p. 571-583.

35 U.S.C. § 103 Rejection

Reconsideration is respectfully requested of the rejection of claims 1, 3-5, 7-17, and 23-32 as being unpatentable over Basinger et al. (Toxicology and Applied Pharmacology, 1990, vol. 108, pages 1-15) under 35 U.S.C. § 103.

Claims 1 and 31

Claim 1 is directed to a method for reducing the incidence of ototoxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound, the method comprising administering to said patient an effective amount of an otoprotective agent comprising methionine.

There are three criteria for establishing a prima facie case of obviousness. First, there must be some reason either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the way the claimed invention does. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach all the claim limitations. Thus, the issue is whether it would have been obvious to treat cisplatin-induced ototoxicity by administration of methionine. The U.S. Supreme Court in *KSR v. Teleflex* relied on predictability of the results as a basis for obviousness by stating that when a combination of known elements by known methods yields predictable results, the invention is likely to be obvious.[3] However, the side effects of cisplatin administration that different patients experience are unpredictable. This is evidenced by the following data. Nephrotoxicity occurred in about 28-36% of patients given a single dose of 50 mg/m^2 cisplatin and ototoxicity occurred in up to about 31% of patients given the same 50 mg/m^2 cisplatin dose.[4] In other studies, fewer patients experienced ototoxicity (e.g., clinical hearing loss) than nephrotoxicity.[5] In these reports, the majority (69% in one report) did not experience ototoxicity. Furthermore, there is much evidence that different causes of ototoxicity have different mechanisms. Thus, there was no basis for predicting that any specific nephroprotectant such as L-methionine might or might not

[3] See *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007); 85 U.S.P.Q.2d 1385, 1395 (2007).
[4] See id.
[5] Planting et al., Cancer Chemotherapy and Pharmacology 1997, 40(4), 347-352.

be effective for ototoxicity. Given the knowledge in the art of the differences in the mechanisms leading to different toxic conditions, one skilled in the art, and therefore aware of these differences, would not have gained any reasonable expectation from the cited references that methionine would act successfully as an otoprotectant for cisplatin administration. Thus, from the differences in the incidence of nephrotoxicity vs. ototoxicity for patients receiving therapeutic doses of cisplatin and the differences in mechanism between nephrotoxicity and ototoxicity, a person of ordinary skill would not have had a reasonable expectation that administration of methionine to a patient receiving a chemotherapeutically effective amount of an anti-tumor platinum coordination compound would reduce the incidence of ototoxicity as required by claims 1 and 31.

Although the Office asserts that the Basinger reference "teaches that ototoxicity is a dose-limiting toxicity associated with cisplatin administration,"[6] this is not an accurate representation of the reference. The Basinger reference states that "[n]ephrotoxicity is generally considered the dose-limiting toxicity in patients treated with CDDP..., although other toxicities can be severe.[7] Further, while it may be true that "a reduction in dose-limiting toxicities would have been a natural result"[8] of administration of L-methionine, Basinger states that nephrotoxicity is considered the dose-limiting toxicity and shows data supporting that L-methionine administration does reduce nephrotoxicity. Thus, Basinger would have taught a person of ordinary skill that the incidence of nephrotoxicity could have been reduced through L-methionine administration, but the unpredictability of the incidence of other toxicities including ototoxicity would not have led a person of skill in the art to contemplate treating ototoxicity using L-methionine administration.

Nor would reduction of the incidence of ototoxicity have "naturally result[ed]" from treatment of nephrotoxicity with methionine. There is no evidence that rats suffered any incidence of ototoxicity, or that they would have but for the administration of methionine. At all events, there is nothing whatsoever in Basinger that would have made it obvious to treat cisplatin-induced ototoxicity with methionine.

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[6] See Office action dated March 27, 2008 at page 3.
[7] See Basinger et al., page 2, left column.
[8] See Office action dated March 27, 2008 at page 3.

Whatever merit there might otherwise be in the Office's assertion that "the effects of administering methionine and CDDP to a patient are not separable from the composition"[9] this proposition entirely misses the point. The instant claims are not to the CDDP composition but instead to a novel method of using a defined composition in the treatment of ototoxicity. The claimed method is met only when the defined otoprotective agent is administered to a patient who has received a dosage of an anti-tumor platinum co-ordination compound that causes ototoxicity, or which would cause ototoxicity in the absence of the agent so defined. As stated by the C.C.P.A in reversing an obviousness rejection of a claim to a method of treating a specified condition with a defined treatment agent based on the inherent effect of treating a different condition with a similar agent.

> [Inherency] is quite immaterial if, as the record establishes here, one of ordinary skill in the art would not appreciate or recognize that inherent result, *in re Shetty*.[10]

A fortiori, there is no basis for obviousness where even latent inherency cannot be shown to have existed in the reference. The method claims at issue in *Shetty* were directed to methods for appetite control and the cited prior art disclosed compounds and dosages useful for combating microbial infestation. The *Shetty* court stated that the Office had "failed to show a reasonable expectation, or some predictability" that the prior art compound disclosed in the first reference would be an effective appetite suppressant if administered in the dosage disclosed in the second reference and that the Office's hindsight assertion that the dosages would make the weight loss method obvious was insufficient.[11] Similar to *Shetty*, claims 1 and 31 recite a method for reducing the incidence of ototoxicity while the reference cited against these claims disclose methods for reducing the incidence of nephrotoxicity. Thus, claims 1 and 31 are patentable over the cited references.

Further, the court in *Ex parte Zbornik* found a process for treating Air Sac Infection in fowl patentable over prior art disclosing substantially the same compound to treat ducks for malaria.[12] The *Zbornik* court found that the claims were patentable because the cited reference was not concerned with appellant's problem and it failed to provide a reason for a person of

[9] See Office action dated March 27, 2008 at page 13.
[10] 195 U.S.P.Q. 753.
[11] See id. at 756.
[12] *Ex parte Zbornik*, 109 U.S.P.Q. 508.

ordinary skill to arrive at the appellant's solution. Similarly, the cited reference is concerned with reducing nephrotoxicity, not ototoxicity, and it fails to provide a reason for a skilled person to expect that methionine would provide otoprotection to a patient undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound.

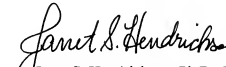
Basinger et al. merely disclose that administration of L-methionine with cisplatin reduces the nephrotoxicity known to arise from cisplatin administration. The reference does not disclose or provide any reasoning why L-methionine or any other composition would or could be effective under any conditions of administration to protect against ototoxicity. The text of Basinger only mentions ototoxicity as a possible side effect of cisplatin administration. To the extent it has any relevance at all, the reference would have provided a person of ordinary skill with the expectation that L-methionine was only effective as a nephroprotectant. Therefore, claims 1, 31, and the claims that depend therefrom satisfy the requirements of 35 U.S.C. § 103(a).

CONCLUSION

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,



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